Workshop on Unapproved Drugs Demonstrating Clinical Drug Safety

January 9, 2007

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Demonstrating Drug Safety– Clinical Considerations

- For an New Molecular Entity (NME), one would want adequate data (controlled and uncontrolled) to allow for a risk-benefit determination
- ICH / FDA guidance asks for a minimum of the following for chronic use drugs indicated for non-life-threatening conditions:
  - 1500 patients exposed overall
  - Data from 300 patients for 6 months, 100 pts for 12 months
  - Extent needed, though, varies by circumstance ***(see Guidance on Pre-marketing Risk Evaluation: www.fda.gov/cder/guidance/6357fnl.htm)***

Demonstrating Drug Safety – Clinical Considerations

- Beginning question for an unapproved drug seeking approval is – what is already known and proven?
  - Has the drug moiety ever been approved (including final monograph or DESI review)?
    - In any indication?
    - In similar/same indication?
  - If not, how much information is known on the use of the drug?
    - Literature (RCTs, case series,…); anecdote

Demonstrating Drug Safety – Clinical Considerations

- If the drug substance was previously approved for the same or similar indication, reliance on previous findings of safety may be possible and would limit (if not negate) need for additional safety data
- If drug substance not previously approved or approval was for an unrelated indication, reliance on literature or other information may decrease amount of added safety data needed
  - If efficacy trials are needed, safety may be well supported, if not fully elucidated, by these trials

Demonstrating Drug Safety – Clinical Considerations

- Note, this advice refers to the active moiety. The drug is not made “different” by salts, esters, dosage form
- Information from the same active moiety from other manufacturers, or from the active moiety in other salts, esters, and/or dosage forms may provide some relevant for the safety assessment

Demonstrating Drug Safety – Clinical Considerations

- Questions for drug substances previously "approved" (including DESI/final mono.):
  - Same route?
  - Same duration / population?
  - Same (or less) exposure/dose?
- These questions will impact on what is "known," and what is "unknown" for proposed indicated use (and therefore needs to be demonstrated/studied)

Demonstrating Drug Safety – Clinical Considerations

- Important point: long-term marketing/use without prior approval and without available, useful data in the literature, may not provide much evidence of safety
  - Lack of defined Adverse Drug Reporting (outside of the Serious ADR reporting required since 1984)
  - Lack of controlled or even uncontrolled, systematic safety evaluations
  - Lack (often) of preclinical (animal) characterization of safety

Demonstrating Drug Safety – Clinical Considerations

- In summary, FDA needs assurance of safety to make decision on risk and benefit
- Risk decision making can be informed by previous findings from products with that drug substance and/or literature data on human (and animal) testing
- “Unknowns” left, after accounting for above, would need to be answered through clinical trials